Building in efficacy: developing solutions to combat drug-resistant *S. pneumoniae*

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ABSTRACT

The development of our understanding of the pharmacokinetic (PK) and pharmacodynamic (PD) principles that determine antimicrobial efficacy has advanced substantially over the last 10 years. We are now in a position to use PK/PD principles to set targets for antimicrobial design and optimisation so that we can predict eradication of specific pathogens or resistant variants when agents are used clinically. Optimisation of PK/PD parameters to enable the treatment of resistant pathogens with oral agents may not be possible with many current agents, such as some cephalosporins, macrolides and fluoroquinolones. Aminopenicillins, however, such as amoxicillin, have linear PK and have a good safety profile even at high doses. The new pharmacokinetically enhanced oral formulation of amoxicillin/clavulanate, 2000/125 mg twice daily, was designed using PK/PD principles to be able to eradicate *Streptococcus pneumoniae* with amoxicillin MICs of up to and including 4 mg/L, which includes most penicillin-resistant isolates. For amoxicillin and amoxicillin/clavulanate, a time above MIC (T > MIC) of 35–40% of the dosing interval (based on blood levels) is predictive of high bacteriological efficacy. This target was met by the design of a unique bilayer tablet incorporating 437.5 mg of sustained-release sodium amoxicillin in one layer plus 562.5 mg of immediate-release amoxicillin trihydrate and 62.5 mg of clavulanate potassium in the second layer, with two tablets administered for each dose. This unique design extends the bacterial killing time by increasing the T > MIC to 49% of the dosing interval against pathogens with MICs of 4 mg/L, and 60% of the dosing interval against pathogens with MICs of 2 mg/L. Based on these results, this new amoxicillin/clavulanate formulation should be highly effective in treating respiratory tract infections due to drug-resistant *S. pneumoniae* as well as β-lactamase-producing pathogens, such as *Haemophilus influenzae* and *Moraxella catarrhalis*.

Keywords Pharmacokinetics, pharmacodynamics, amoxicillin/clavulanate, drug development

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INTRODUCTION

There is no question that the introduction of antimicrobials to treat bacterial infection has greatly reduced morbidity and mortality in respiratory tract diseases. However, only one placebo-controlled trial of antimicrobial therapy in community-acquired pneumonia (CAP), a study by Evans and Gaisford, published in 1938, is known to this author [1]. This randomised study compared one of the initial sulfonamides with what was, at the time, standard, nonspecific supportive treatment in patients who would now be regarded as having severe disease. Mortality was significantly reduced in the patients receiving sulfonamide (8%) compared with controls (27%) (Fig. 1) [1]. It is also interesting to note that there was a significant effect of age in this study, with mortality in the control group being 50% in patients 40 years of age or older, compared with 16% in patients under 39 years of age. Due to the high mortality associated with CAP of this type, it is no longer considered ethical to perform placebo-controlled studies, although milder forms of CAP in outpatients have virtually

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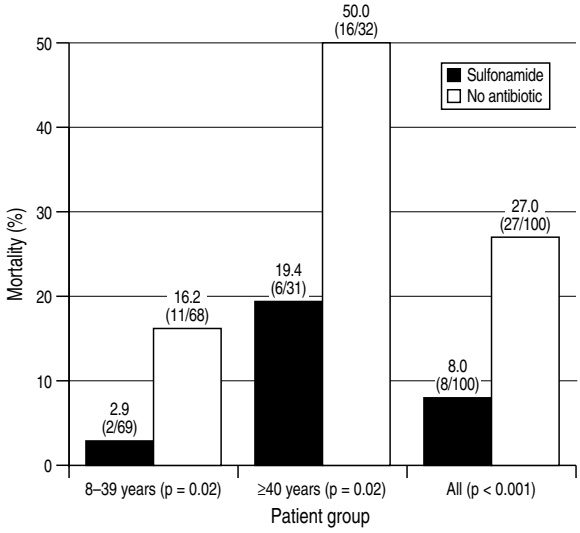

Fig. 1. Mortality in hospitalised patients with lobar pneumonia: sulfonamide vs. no treatment. Adapted from reference 1.

no mortality [2]. Morbidity remains a concern, however, in CAP, even when the associated risk of mortality is low, but there is little information on this subject. Clinical trials that could show a significant difference between antibacterial therapies require very large numbers of patients, particularly in studies of acute exacerbations of chronic bronchitis, sinusitis and otitis media, where rates of spontaneous recovery are high [3,4]. Thus, the majority of clinical trials are designed to show only noninferiority of a new agent compared with existing therapies. The limitation of this approach is that we have very little clinical information that can indicate whether one antibacterial is clinically more effective than another, or even more effective than placebo. In fact, statistically similar outcomes between drugs in a noninferiority trial do not guarantee equivalency, only that the study was not powered to show differences in efficacy.

Without a control group against which efficacy can be judged, it is difficult to evaluate new agents. Knowledge of the natural history of the disease being studied is helpful, but in most diseases this is not fully known, or was determined before the antibacterial era and so may no longer be relevant. Antimicrobial resistance to currently used agents among the key respiratory pathogens is common world-wide, and the prevalence is increasing [5]. It is now clear, certainly in CAP [6–8], and also from double tympanocentesis studies in otitis media [9–11], that antimicrobial resistance is having a negative impact on clinical outcomes. Now, more than ever, it is essential that we know which agents will have optimal antibacterial efficacy. Moreover, as resistance increasingly compromises the effectiveness of currently available agents, and with a lack of new agents likely to be available soon, there is a need to optimise the way in which we use existing agents.

Until recently, setting breakpoints predictive of bacterial efficacy was based on in-vitro measures, such as MIC distributions and inadequate clinical studies. Over the last decade, however, our understanding of the relationship between pharmacokinetics (PK) and pharmacodynamics (PD) has expanded considerably (see MacGowan, this issue). PK/PD parameters have been found to correlate with bacterial and clinical outcomes [12]. We are now in a position where we can use our greater understanding of PK/PD to direct the development of new antibacterials and to optimise existing formulations to guide therapy choices [12–14].

OPTIMISATION OF CURRENTLY AVAILABLE ANTIBIOTICS USING PK/PD

Antibacterials have been shown to have either time-dependent or concentration-dependent efficacy (Table 1) [15–17]. For antimicrobials whose bacteriological efficacy is time-dependent, the PK/PD parameter that most closely correlates with efficacy is the duration of the dosing interval for which serum concentrations exceed the MIC (T > MIC) [18]. For drugs with concentration-dependent killing, the ratio of either the area under the serum concentration–time curve to the MIC (AUC:MIC) or the peak serum concentration to the MIC (C_{max}:MIC) are most predictive of bacteriological efficacy [18]. Once the magnitude of the PK/PD parameter required for maximal bacteriological efficacy has been determined, it can be used to predict whether a given agent will be effective against pathogens with a given MIC. The magnitude of the PK/PD parameter needed to attain maximal antimicrobial efficacy is similar in animals and humans, therefore animal models can also be used to predict antimicrobial activity in humans [18,19]. In addition, double tympanocentesis studies in otitis media allow PK/PD predictions to be verified clinically, because middle

Table 1. PK/PD parameters predictive of antimicrobial efficacy, based on unbound plasma levels [15–17]

Antimicrobial effect	PK/PD parameter	PK/PD target	Antimicrobial class
Time-dependent killing and minimal/moderate persistent effects	Proportion of dosing interval for which unbound serum drug level is above MIC (T > MIC)	Unbound serum concentration present for > 40–50% of the dosing interval	Carbapenems Cephalosporins Monobactams Oxazolidinones Penicillins
Time-dependent killing and prolonged persistent effects	Unbound 24-h serum AUC:MIC ratio	Unbound serum 24-h AUC:MIC ratio > 25–30 (immunocompetent) or > 100 (immunocompromised)	Streptogramins Tetracyclines Vancomycin Erythromycin[a] Azithromycin Clarithromycin Clindamycin Ketolides[b]
Concentration-dependent killing and prolonged persistent effects	Unbound 24-h serum AUC:MIC ratio or peak:MIC ratio	Unbound serum 24-h AUC:MIC ratio > 25–35 or peak:MIC > 3 (immunocompetent) or; unbound serum 24-h AUC:MIC ratio > 100 or C_{max}:MIC > 10 (immunocompromised)	Fluoroquinolones Aminoglycosides

[a]Please see the main text for a discussion regarding the appropriate PK/PD parameter for erythromycin and other macrolides.
[b]Telithromycin has been shown to have concentration-dependent activity *in vivo*, but its PD parameters have not been adequately established and may be different from other agents in this group [17].

ear fluid is obtained for culture before and then 3–5 days after antimicrobial therapy has started. Thus, clinically verified PK/PD targets can be set for the optimisation of antibacterials, and the ability of different agents to achieve these targets can be assessed. The capacity to optimise an antibacterial based on PK/PD will depend upon several factors, including the MIC of the target organism, the PK (and how easy this is to manipulate), as well as the safety profile of the drug.

Macrolides and azalides

Until recently, macrolides were thought to exhibit time-dependent, and azalides concentration-dependent, antibacterial activity. Craig and colleagues, however, have recently suggested that bactericidal activity of all macrolides, azalides and ketolides is concentration-dependent [16]. In this study, a 24-h AUC:MIC ratio of at least 16.4–26.4, based on unbound serum concentrations, was predictive of maximal bacterial eradication for erythromycin, clarithromycin, 14-hydroxy-clarithromycin, roxithromycin, azithromycin, ABT-773, HMR6004 and clindamycin against a standard strain of *Streptococcus pneumoniae*. Other studies, however, have shown erythromycin to be time-dependent, and azithromycin and clarithromycin to be concentration-dependent, with C_{max}:MIC ratio being the best predictor of activity [20,21]. Studies such as these allow PK/PD breakpoints to be calculated that predict the MIC cut-offs for maximal bacterial eradication. For example, a recent study by Hoffman *et al.* in a mouse model of pneumococcal pneumonia indicated a PK/PD breakpoint of 1 mg/L for clarithromycin [22]. This study showed that after 84 h, survival in mice treated with doses simulating human PK was generally ≥50% for strains with an MIC up to 1 mg/L, which included macrolide-susceptible isolates and some *mef*(A)-containing isolates, while survival was usually <40% for *erm*(B)-containing strains and with *mef*(A)-containing strains where MICs were >4 mg/L (Fig. 2a) [22]. Azithromycin was also tested in this model, with a PK/PD breakpoint of ≤0.12 mg/L determined, which differentiated between macrolide-susceptible strains and macrolide-resistant strains with either resistance mechanism (Figure 2b) [22]. Clinical verification of PK/PD breakpoints for macrolides is available for azithromycin from double tympanocentesis studies in otitis media [9,23]. In these studies, the rate of bacteriological failure of azithromycin against strains of *S. pneumoniae* with MICs >0.25 mg/L was 78.6% (11/14 isolates) [9,23], a rate similar to the value of 84% (48/57) obtained with placebo over 30 years ago [24]. In contrast, for strains of

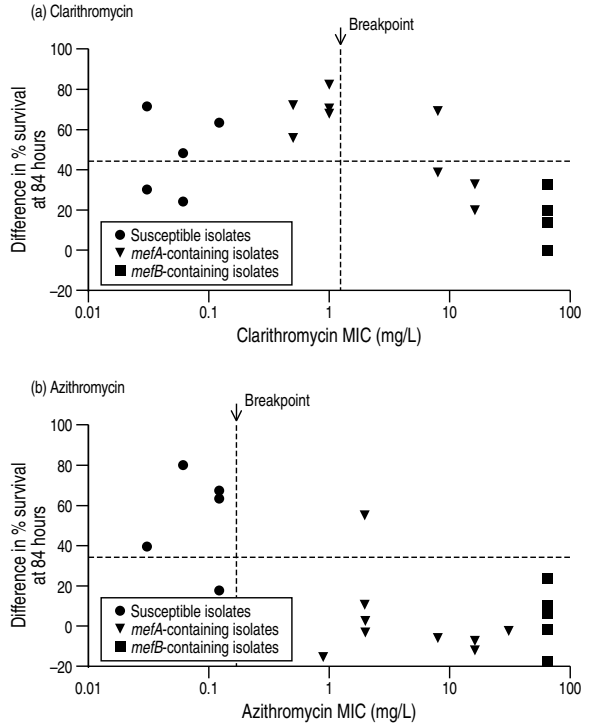

Fig. 2. Correlation between MIC for (a) clarithromycin and (b) azithromycin against *S. pneumoniae* and end-of-treatment survival in a mouse model simulating human PK. Adapted from reference 22.

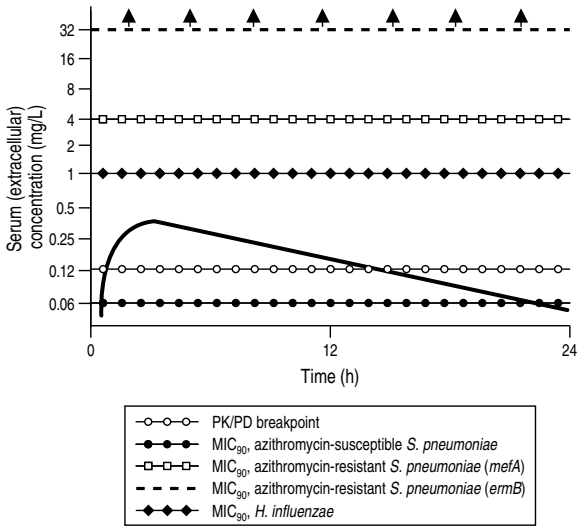

Fig. 3. Use of PK/PD breakpoints to predict efficacy of azithromycin against azithromycin-susceptible *S. pneumoniae*, azithromycin-resistant *S. pneumoniae* with either *mef*(A) or *erm*(B), and *H. influenzae*. Adapted from reference 26.

S. pneumoniae with azithromycin MICs of ≤0.25 mg/L, the bacteriological failure rate was only 5.4% (2/37) [9,23]. These data indicate that the clinically derived breakpoint for azithromycin should be between 0.12 mg/L and 1 mg/L [25]. Against *Haemophilus influenzae*, for which most azithromycin MICs are > 1 mg/L, the bacteriological failure rates in otitis media are again similar to those of placebo for this species (61.7% [50/81] vs. 52% [13/25], respectively) [9,23,24]. Thus, for azithromycin, the currently available formulation would result in suboptimal bacteriological efficacy against *S. pneumoniae* with macrolide resistance associated with either *erm* or *mef*, and against virtually all strains of *H. influenzae* (Fig. 3) [26].

As discussed above, there are two major mechanisms of macrolide resistance among *S. pneumoniae*. The *mef*(A)-mediated efflux mechanism (M-phenotype resistance) confers resistance to macrolides but isolates remain susceptible to clindamycin vs. the *erm*(B)-mediated methylation mechanism (MLS_B-phenotype resistance) for which strains are resistant to both macrolides and clindamycin. Strains possessing *mef*(A) have erythromycin, azithromycin and clarithromycin MICs of, typically, 2–16 mg/L, whereas strains with *erm*(B) have MICs as high as ≥256 mg/L [5,27–29]. For *H. influenzae*, MIC values for all the macrolides and azalides are similar to those seen in *S. pneumoniae* strains with efflux-mediated resistance, and it is now known that a macrolide efflux mechanism is present in the majority of *H. influenzae* strains [5,30].

In animal models, it is possible to increase the dose of macrolides and azalides to meet the PK/PD target for eradication of *S. pneumoniae* strains with MICs in the range conferred by *mef*(A) resistance and most strains of *H. influenzae* [31]. In humans, however, limitations in PK are combined with safety issues that arise with increased dosages, making optimisation difficult. As a consequence, it is not possible to achieve doses in humans that would meet the PK/PD target for eradication of these strains (Fig. 3) [26]. Options for the optimisation of macrolides and azalides are therefore limited. Already, in areas of high macrolide resistance prevalences, such as Spain and the USA, clinical failures have been seen in pneumococcal pneumonia for strains with either *mef*(A) or *erm*(B) resistance mechanisms [7,32]. Thus, if the prevalence of macrolide resistance continues to increase, these agents will lose even more of their clinical utility.

Quinolones

The PK/PD parameter predictive of quinolone efficacy is the unbound serum AUC:MIC ratio or unbound serum C_{max}:MIC ratio [18]. In animal infection models, an AUC:MIC ratio of approximately 35 produces a bacteriostatic effect and this is independent of the dosing interval, the site of infection or the fluoroquinolone agent used [18]. Mortality in animal models, for both Gram-positive and Gram-negative infections, can be prevented with AUC:MIC ratios of ≥100. Mortality in these models is >50% for AUC:MIC ratios of less than 30 [33]. In one of the very few PK/PD clinical studies ever conducted in humans where levofloxacin in respiratory tract and other infections was studied, clinical failure rates were 43% for AUC:MIC ratios of <25, 11.5% for AUC:MIC ratios of 25–100 and 1% for ratios in excess of 100 [34]. For levofloxacin, PK studies demonstrate mean AUC values, which vary somewhat with age and sex, of 47.5–74.7 mg·h/L (33.3–52.3 mg·h/L based on free drug) for the 500 mg daily dosing regimen and 90.7–110.0 mg·h/L (63.5–77.0 mg·h/L based on free drug) for the 750 mg daily dosing regimen. These provide PK/PD breakpoints of 1.3–3.1 mg/L for an AUC:MIC target ratio of 25 and 0.3–0.7 mg/L (based on free drug values) for an AUC:MIC target ratio of 100. A target AUC:MIC ratio of 25 is thought to be sufficient for less severe infections in immunocompetent patients, while a target AUC:MIC ratio of >100 is needed for more severe infections or for immunocompromised patients [34,35]. The levofloxacin MIC_{90} for *S. pneumoniae* is 1 mg/L [5], therefore >90% of isolates will be susceptible based on levofloxacin achieving AUC:MIC ratios of ≥25, but not based on ratios of ≥100.

Fluoroquinolone resistance develops in a stepwise fashion, through accumulation of mutations in the quinolone resistance-determining regions of DNA gyrase and topoisomerase IV. Currently, there is little resistance to quinolones among pneumococcal isolates, although this is increasing in some regions [5,36]. Maintaining this low prevalence of quinolone resistance is important, because once a strain becomes resistant, the activity of most, if not all, of the quinolones is compromised. To meet PK/PD targets for resistant strains, the total daily dose would need to be increased, which is best achieved by increasing the single daily dose rather than increasing the frequency of dosing, because quinolones are concentration-dependent agents [18]. The fluoroquinolones, however, have a relatively narrow safety window, limiting the options for increasing the dosage and frequency, and most currently available agents would not be able to overcome quinolone resistance in *S. pneumoniae* while still maintaining acceptable safety/tolerability profiles. Where quinolone-resistant pneumococci do exist, newer quinolones may be able to achieve the necessary AUC:MIC ratio for one-eighth to one-half of isolates with single-step mutations, but the established and commonly used quinolones, ciprofloxacin and levofloxacin, demonstrate very little activity against any of these strains [36,37]. In addition, despite the low prevalences of quinolone resistance, clinical failures due to quinolone resistance have been reported for levofloxacin, including the on-therapy selection of resistant strains [8]. Thus, once a quinolone-resistant strain becomes established in an area, the clinical value of the quinolones becomes questionable.

β-Lactams

All β-lactams display time-dependent bacteriological activity, so the T > MIC is the relevant PK/PD parameter [18]. In animal models of *S. pneumoniae* infection, a T > MIC of 40–50% of the dosing interval is required to prevent mortality for cephalosporins and >40% for penicillins [38]. Clinical studies in otitis media and sinusitis also show maximal bacterial eradication with T > MIC values >40% [39].

Increases in penicillin resistance in *S. pneumoniae* world-wide are of concern [5]. A recent case–control study by Ailani *et al.* found that cephalosporin resistance in *S. pneumoniae* increased the time required to respond to treatment and the length of hospital stay [40]. There were no differences, however, in mortality in this study between patients with cephalosporin-susceptible vs. -resistant strains [40]. For the oral cephalosporins, limitations in PK, primarily the lack of linear PK, prevent the possibility of sufficiently increasing T > MIC to cover penicillin-resistant strains by increasing dosing or dosing frequency. A study by Urban *et al.* evaluated dosing of cefpodoxime in the mouse thigh model with *S. pneumoniae* [41]. In this model, it

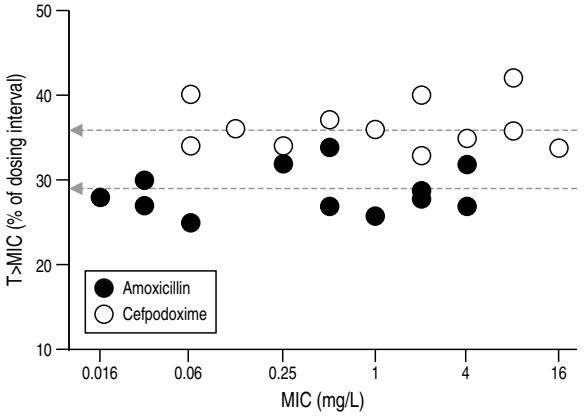

Fig. 4. Relationship between MIC and T > MIC for maximal bacterial eradication: amoxicillin and cefpodoxime against *S. pneumoniae* in a mouse thigh model. Adapted from references 41 and 42. Broken arrows indicate T > MIC required to maintain efficacy.

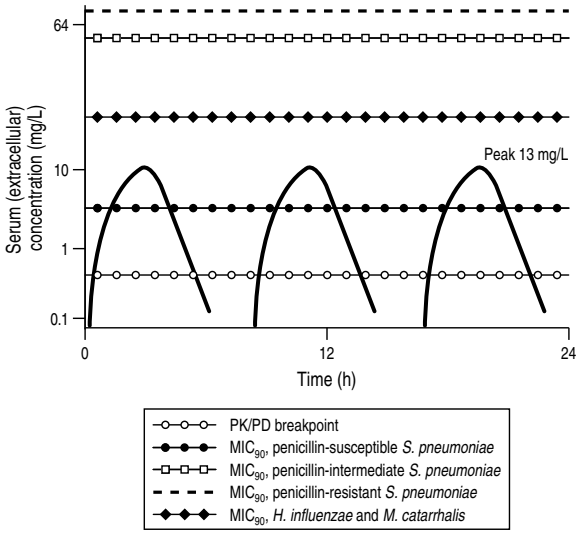

Fig. 5. Use of PK/PD breakpoints to predict efficacy of cefaclor against penicillin-susceptible *S. pneumoniae*, penicillin-intermediate *S. pneumoniae*, penicillin-resistant *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Adapted from references 43 and 44.

was possible to increase doses of cefpodoxime to cover strains with an MIC of ≥1 mg/L for ≥30% of the dosing interval. However, the doses necessary to reach this level of coverage would not be achievable in humans (Figure 4) [41,42]. Cefaclor provides another example of the difficulties in achieving the necessary T > MIC with some cephalosporins. Although the peak concentration of cefaclor provided by the standard twice daily and three times daily dosing regimens is 13 mg/L, the very short half-life of this drug means that the concentration present for 40–50% of the dosing interval is only 0.5 mg/L. With a PK/PD breakpoint of 0.5 mg/L, cefaclor can only reliably cover the most sensitive penicillin-susceptible strains of *S. pneumoniae*, whereas penicillin-intermediate and -resistant *S. pneumoniae* and *H. influenzae* and *Moraxella catarrhalis* are not covered at this breakpoint (Figure 5) [43,44]. The low efficacy for cefaclor predicted by this PK/PD breakpoint has been borne out in clinical studies in otitis media, in which cefaclor was shown to have failure rates similar to those of placebo against penicillin-intermediate and -resistant *S. pneumoniae* and *H. influenzae* [25].

For penicillin given at high doses intravenously, there is still no proven case of failure in pneumococcal pneumonia due to penicillin resistance and no strong evidence for an effect of penicillin resistance on patient outcomes [32]. The main reason for this is that penicillin can be given at very high doses, extending the T > MIC and therefore covering 'resistant' pathogens. Thus, unlike other classes of antimicrobial, optimising the PK by increasing T > MIC is possible with the penicillins, including oral agents such as amoxicillin, by increasing the dose, increasing the dosing frequency or enhancing the PK by other means.

DEVELOPMENT OF A PHARMACOKINETICALLY ENHANCED FORMULATION OF AMOXICILLIN/CLAVULANATE

The standard adult dose of amoxicillin/clavulanate in many countries is 875/125 mg, given twice daily. At this dose, the peak amoxicillin concentration is similar to that of cefaclor, at 12 mg/L, but at least 2 mg/L of amoxicillin is present for ≥40% of the dosing interval (Fig. 6, Table 2) [13,44–46]. For *S. pneumoniae*, a PK/PD breakpoint of 2 mg/L for amoxicillin/clavulanate covers all penicillin-susceptible strains with approximately a 100-fold safety margin. This formulation is also effective against penicillin-intermediate strains and some, but not all, penicillin-resistant strains. This breakpoint is also above the MIC_{90} for *H. influenzae* and *M. catarrhalis*, and the clavulanate provides coverage of β-lactamase-positive strains. Despite the coverage achieved with the

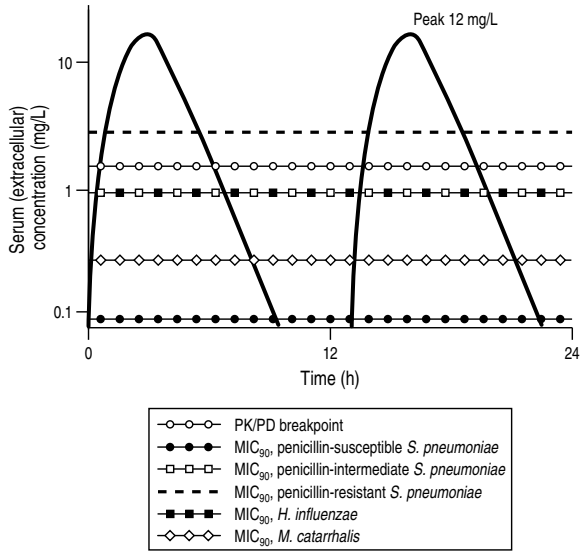

Fig. 6. Use of PK/PD breakpoints to predict efficacy of amoxicillin/clavulanate 875/125 mg against penicillin-susceptible *S. pneumoniae*, penicillin-intermediate *S. pneumoniae*, penicillin-resistant *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Adapted from reference 44.

Table 2. T > MIC (as percentage of dosing interval) achieved with four amoxicillin/clavulanate formulations [13,45,46]

Amoxicillin/clavulanate formulation	T > MIC (% of dosing interval) for amoxicillin MIC (mg/L):			
	1	2	4	8
875/125 mg twice daily	44	40	26	–
875/125 mg three times daily	69	57	34	–
1000/125 mg three times daily	> 65	55	41	–
2000/125 mg twice daily[a]	> 70	60	49	35

[a]Amoxicillin component contains immediate-release amoxicillin trihydrate equivalent to 562.5 mg amoxicillin and sustained-release crystalline sodium amoxicillin equivalent to 437.5 mg amoxicillin.

currently available dosage of amoxicillin/clavulanate, penicillin-resistant *S. pneumoniae* are becoming more common, including strains with amoxicillin MICs of >2 mg/L [5]. With the 875/125 mg twice daily standard dose of amoxicillin/clavulanate, the T > MIC is only 26% of the dosing interval for bacterial strains with amoxicillin MICs of 4 mg/L (Table 2) [13,46].

The PK/PD characteristics of amoxicillin/clavulanate are well known [46]. In order to develop a new formulation that would maximise eradication and, therefore, efficacy against penicillin-resistant *S. pneumoniae*, a target T > MIC of >40% was set for strains with amoxicillin MICs of 4 mg/L. In order to achieve this, there was a number of issues that had to be considered. Increasing the T > MIC by simply increasing the dose of amoxicillin/clavulanate is possible for intravenous or suspension formulations, but for the tablet form there are constraints for tablet size or the number of tablets that a patient can take at a time. Increasing the peak serum concentrations may also increase the number of adverse events patients experience. PK could also be improved by increasing the dosing frequency. This approach has already been adopted in Spain with the 875/125 mg three times daily formulation, and in France with a 1000/125 mg formulation being administered twice daily for acute exacerbations of chronic bronchitis and three times daily for CAP, in response to recommendations in these countries for amoxicillin use (Table 2) [46]. However, maintaining the convenience of a twice daily dosing schedule would be desirable. Finally, the amount of clavulanate must be maintained at a level where it provides coverage of β-lactamases, but not so high as to increase the potential for gastrointestinal side-effects of this compound.

The question then arises of just how the T > MIC can be extended to cover strains with amoxicillin MICs >2 mg/L while maintaining a twice daily dosing schedule, β-lactamase coverage and an adverse event profile similar to that of conventional formulations. This question was addressed by developing a novel form of bilayer tablet containing an immediate-release amoxicillin/clavulanate layer and a sustained-release amoxicillin layer. The immediate-release portion of the tablet contains amoxicillin trihydrate equivalent to 562.5 mg of amoxicillin and potassium clavulanate equivalent to 62.5 mg of clavulanic acid [45]. The sustained-release layer contains crystalline sodium amoxicillin equivalent to 437.5 mg of amoxicillin, which has a longer half-life than the trihydrate. This new pharmacokinetically enhanced 2000/125 mg amoxicillin/formulation is given as two tablets twice daily [45]. As for the majority of oral formulations, the unit dose of clavulanate has remained 125 mg in the new formulation, this amount being sufficient to inhibit the clinically relevant target

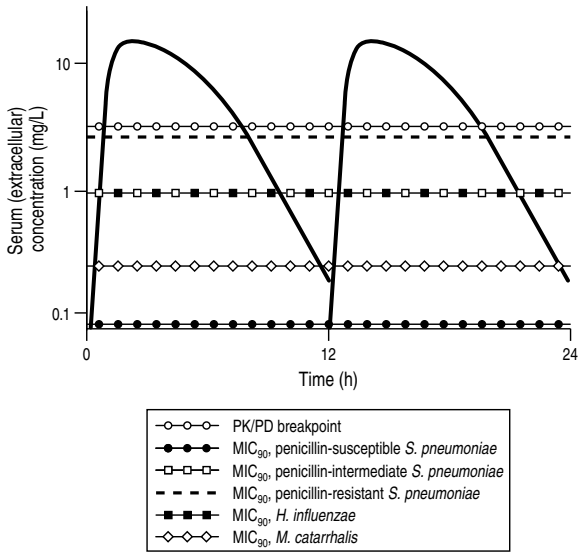

Fig. 7. Use of PK/PD breakpoints to predict efficacy of amoxicillin/clavulanate 2000/125 mg against penicillin-susceptible *S. pneumoniae*, penicillin-intermediate *S. pneumoniae*, penicillin-resistant *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Adapted from references 44 and 45.

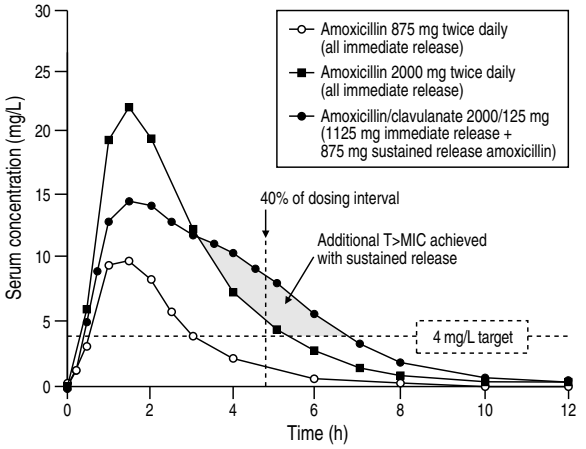

Fig. 8. Target T > MIC and T > MIC achieved with various amoxicillin/clavulanate formulations. Adapted from references 13 and 45.

β-lactamases and protect the amoxicillin component [47]. Although clavulanate does have some antibacterial activity *in vitro*, the addition of clavulanate does not affect the PK/PD profile of amoxicillin against *S. pneumoniae* [48]. Amoxicillin/clavulanate 2000/125 mg twice daily achieves a peak concentration of amoxicillin similar to conventional formulations [45]. Due to the sustained-release amoxicillin component, however, the decline in concentration over time is not as steep as conventional formulations, thus enhancing the PK and extending the T > MIC to 49% of the dosing interval for strains with amoxicillin MICs of 4 mg/L and 35% for strains with MICs of 8 mg/L (Figures 7 and 8, Table 2) [13,44–46]. In contrast, just increasing the dose of amoxicillin to 2000 mg, all immediate-release, would only achieve a T > MIC of 35% against strains with amoxicillin MICs of 4 mg/L (Figure 8) [13,45].

CONCLUSIONS

Many currently available antimicrobial agents, or currently available formulations of these agents, do not have adequate PK/PD to achieve bacterial eradication of common respiratory pathogens, including antibacterial-resistant strains. The prevalence of antimicrobial resistance is increasing world-wide, therefore new agents designed specifically to target these organisms are needed. It is unlikely, however, that any new antibacterials with substantially increased efficacy against resistant respiratory pathogens are to become available in the short or medium term.

PK/PD parameters are predictive of bacteriological and clinical outcomes, and can be used to optimise antibacterial dosing regimens. PK/PD parameters can also be used in the formulation of new antimicrobials to combat resistant pathogens and the continuing evaluation of currently available agents. Animal models have demonstrated the predictive value of PK/PD parameters, and clinical studies, such as those in otitis media, have confirmed that these PK/PD parameters are also valid predictors of efficacy in humans [15,25].

Designed using PK/PD targets, a new formulation of amoxicillin/clavulanate (2000/125 mg twice daily) has been developed as a novel bilayer tablet incorporating sustained-release technology [45]. This new formulation achieves a mean T > MIC of 49% of the 12-h dosing interval for amoxicillin MICs of 4 mg/L [45]. This is predictive of high bacteriological efficacy against not only penicillin-susceptible and -intermediate strains of *S. pneumoniae*, but also against the majority of penicillin-resistant strains [46]. The combination of amoxicillin with clavulanate ensures coverage of β-lactamase-producing *H. influenzae* and *M. catarrhalis* [47]. Clinical trials of this new pharmacokinetically enhanced formulation of amoxicillin/clavulanate in a variety of

respiratory illnesses, including those caused by resistant strains, are reviewed in this issue (see Garau, this issue) [49–52].

Utilizing PK/PD represents an effective way of optimising currently available antibacterials, thus retaining our ability to treat difficult pathogens such as penicillin-resistant *S. pneumoniae* in an environment of increasing antibacterial resistance.

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